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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,036	07/30/2001	Kiran Madura	266/165	1466

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/918,036	**Applicant(s)** MADURA KIRAN	
	Examiner Malgorzata A. Walicka	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED Feb. 25, '05 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, second.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *6,7,9,10 and 12*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see the attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Advisory Action

1. Objections

Objection to claim 10 is withdrawn because the claim has been amended.

2. Rejections

2.1. 35 USC, section 112, second paragraph

Rejection of claim 11 is moot because the claim has been canceled. Rejection of claim 6-7, 9-10 and 12 for using the indefinite term "proliferative potential" is withdrawn, because the claims have been amended.

Claims 6-7, 9–10 and 12 are indefinite because they recite the term "rate of proliferation" which is not defined by the claims or specification. The indefinite term renders the claims indefinite.

2.2. 35 USC, section 112, first paragraph

2.2.1. Lack of written description

Rejections maintained or caused by amendment

Claim 10 and 12 and dependent claims were rejected in the previous Office Action as being generic and lacking written description of all the species of ubiquitin-like domains used in fusion proteins. This rejection is now withdrawn because the claims specifically recite sequence identification numbers of the UbL domains used for constructing the proteins.

Claim 6, 7, 9-10 and 12 are rejected for lack of description of assessing the rate of proliferation a cell. The term "rate of proliferation" as used in the art refers to generation time of cell population. The shorter generation time the higher rate of proliferation. The rate of proliferation is quantified by a value that is reciprocal to the generation time or in case of *in vitro* cell culture, ~~to the~~ reciprocal of the doubling time. On page 16, lines 20-34 Applicants refer to "aberrant growth rate" and "cell growth rate". Even if one assumes the "rate of proliferation" can be substituted with "growth rate", the specification fails to provide evidence that the time of degradation of the claimed fusion proteins is related to the proliferation rate of any cell culture. Applicants disclose, for example in Figure 6A, 7A and 9B, that Rad23$^{1-369}$, Rad23-HA and Ubl ^{R23}-lacZ are not detected within 0-30 min. after labeling in some cells; i.e., they are degraded. These data are not sufficient to be a base for any routine determination of rate of proliferation of any cell, as necessary in a clamed method. Applicants do not demonstrate any correlation between the generation time, or growth rate constant (ln2/population doubling time), of cell population and the rate of degradation of the fusion proteins, containing Ubl domain and a reporter protein, which were transfected to the cells of said population. Furthermore, as emphasized in the final rejection, the kinetics of degradation of the fusion protein containing Ubl domain and a reporter protein seems to depend on cell used and details of degradation measurements, as well as on the fusion protein itself; see the data for the cells temporarily arrested in their growth, page 33, line 34 of the specification. The scope of the claims does not exclude such cells from the the application of the claimed method. Furthermore, some exponentially growing cells

that do not degrade fusion proteins comprising Ubl and a reporter gene; see results for ufd5Δ mutant (Fig. 10E), page 36, line 13, cim5-1 cells (Fig. 11B) page 37, line 6 and pre1-1 pre2-2 cells (Fig. 11A), page 37, line 13. In summary, the one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

Applicant traverses the above rejection as follows:

> "Applicant respectfully disagrees with the Examiner's interpretation of the data presented at page 32, line 26 of the specification. This data indicates that unlike Rad23-HA (a protein having a UbL domain; i.e., SEQ ID NO:3), R-ßgal and Ub-P-ßgal are efficiently degraded in both exponential and stationary phases of growth. R-ßgal and Ub-P-ßgal are fusion proteins of *ubiquitin itself* and ßgal, not protein having a Ubl domain as set forth in the instant claims. See, for example, page 39, lines 15-18. Therefore, the stability of R-ßgal and Ub-P-ßgal are fusion proteins in exponential and stationary phases of growth is not indicative of the stability of claimed Ubl domain-containing proteins under the same growth conditions" the third page of the REMAKS, second paragraph.

Applicant's argument have been fully considered, but rejection made in the previous Office Action was correct because:

1) ubiquitin by definition is a protein containing a Ubl domain, because it is the polypeptide being the most ubiquitin like,

2) the language of claims did not exclude Ub form the claimed fusion proteins.

However, currently amended claims are limited to Ubl domains of explicitly stated structures, SEQ ID NO:2-12 that do not contain the entire Ub, therefore the previous rejection and Applicant's argument are moot.

Applicant further emphasize, "upon reading the disclosure as a whole, one of skill in the art would appreciate that the utility of the claimed constructs and methods of invention is in the assessment of the *general* [Applicant's emphasis] rate of proliferation of cell. See page 16, lines 20-34", third page, second paragraph of the REMARKS.

This argument is not persuasive because it is unknown what the term "general rate of proliferation" means absent of its definition in Applicants REMARKS or disclosure. The quoted passage of the specification reads as follows:

> "Malignant cells display aberrant growth properties and do not respond to normal regulatory signals. Malignancy therefore arises because aberrant cells continue to grow in conditions when normal cells remain quiescent. Detection and treatment of disorders must begin with the clear identification of cells that manifest aberrant growth

rates. Although malignant cells are often morphologically distinguishable from their wild type counterparts, a quantitative measurement of the growth properties of cells is lacking.

In another embodiment of the present invention, methods are provided which employ Ubl^{R23}-lacZ fusion protein(s) to assess cell growth rates in evolutionary divergent organism from yeast to human."

Although one skilled in the art may assume that the rate of growth can be equivalent to the rate of proliferation, the assessing of rate of growth of any cell line is not taught by the disclosure. Thus, the claims are rejected for lack of written description.

In addition, Applicant's opinion is that ufd5Δ mutant (Fig. 10E), page 36, line 13, cim5-1 cells (Fig. 11B) page 37, line 6 and pre1-1 pre2-2 cells (Fig. 11A), page 37, line 13, are conditional mutants that are sick and unviable, thus not the proper cells to be used in the method; page 4 of REMARKS, line 6 and further. This argument is not persuasive, because the claimed method encompasses use of any cell. Applicant do not exclude specifically ufd5Δ mutant, cim5-1 cells, pre1-1 pre2-2 or an other cells from the scope of the claims.

2.2.2. Scope of enablement

Claim 6-7 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for degradation of $Rad23^{1-369}$, Rad23-HA and Ubl

^{R23}-lacZ within 0-30 min. after labeling when the labeling is performed in some exponentially growing yeast transformants (Fig. 7 and 9), does not reasonably provide enablement for assessment of rate of proliferation of any cell using any fused DNA encoding a protein consisting of Ubl domain of SEQ ID NOs: 2-12, a linker and a reporter protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for assessing the rate of proliferation of cells by using DNA constructs encoding fusion proteins whose function is to be used in said method.

The nature and breadth of the claimed invention encompasses any DNA construct encoding for Ubl-reporter, wherein Ubl is any one of SEQ ID NO: 2-12 operably linked to any reporter, or any Ubl operably linked to reporter that is identified by claims 9 and 12 wherein said proteins are used in a method of assessing the proliferative potential of any cells.

The art of construction of DNA molecules encoding for fusion proteins is highly developed and skills of artisan high, however, because Applicants do not show any correlation between the rate of proliferation of any cell and kinetics of degradation said fusion protein one skilled in the art is forced to perform undue experimentation with low probability of success.

Since the degradation of any fusion protein in any multiplying cell is not disclosed, one skilled in the art would not know which fusion protein, i.e. its encoding

DNA, and which cell type to select for the method. As exemplified in the specification for yeast cells (Sacharomyces cerevisiae) the mechanism of degradation of fusion proteins is complex and involves so called N-end rule pathway and UFD pathway (Ub fusion degradation). Degradation of a particular Ubl-reporter fusion depends on these two pathways and is affected by mutations in any of the genes in the pathways. The degradation also depends on primary and mutated structure of a Ubl used for fusion. In addition, the degradation depends on the link between the Ubl and the reporter. US patent 5,132,213 (quoted by examiner in the last Office action) discloses in Table 2, column 18 that the construct Ubl-Lys-ßgal has in S. cerevisiae the half-life of 3 min, but Ubl-Met-Lys-ßgal more than 20 h; see Fig. 6 of the Patent. Thus, the half-life of any particular construct depends on its structure. In addition, Applicants themselves teach that whereas some yeast cells in logarithmic phase degrade the fusion proteins, other yeast cells do not degrade said fusion protein when they are in the exponential phase of culture; see the above rejection for lack of written description. In addition, the specification is silent as to mammalian cells suitable for use of the method, becuase specification lacks such data. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the fusion proteins had the function to be used in the method for assessing the proliferative potential of any cells. The disclosure fails to provide such guidance of the structure of DNA encoding fusion proteins and the guidance as to the type of cells for which the use of said DNA is applicable; in result,

experimentation left to those in the art has low probability of success and is improperly extensive and undue.

Regarding the emphasizing by the examiner that the degradation rate depends on the link between the Ubl and the reporter, as shown in US patent 5,132,213, Applicants position is the patent focuses on ubiquitin itself (falling outside the scope of the instant invention) and not ubiquitin–like domains. Therefore, according to Applicant, these teachings may not be reliably used to establish a correlation between structure and stability of ubiquitin containing protein.

The state of art does not provide any reason to assume that an exponentially growing cell, for some particular reasons **will not degrade** certain fusion protein containing ubiquitin (a 76 amino acid polypeptide), linker and reporter gene, but the same exponentially growing cell **will always degrade** fusion proteins containing Ubl of SEQ ID NOs: 2-12 (consisting of 75-100) amino acids), any linker and any reporter gene, in a consitent way necessary for the use of the claimed method.

3. Conclusion

All claims remain rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-

0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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